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Arthritis, Rheumatic Diseases, and Related Disorders

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ARTHRITIS, RHEUMATIC DISEASES, AND RELATED DISORDERS

Over 31 million people in the U.S. suffer from arthritis and related rheumatic diseases. Representing about 15 percent of the population, arthritis victims are afflicted with one of 100 or more different types of diseases of the joints and connective tissues. Symptoms range from mild pain in the joints of fingers, hands, or knees, to severe crippling and pain that leave a person totally disabled.

The most frequently crippling form is rheumatoid arthritis, a disease marked by chronic inflammation and overgrowth of the joint linings, destruction of joint cartilage and erosion of bone, leading in many patients to joint deformities.

Degenerative joint disease (osteoarthritis) is by far the most common form of arthritis, afflicting an estimated 16 million persons in the U.S. Characterized by a breakdown of cartilage and changes in the bone, it most commonly develops in the fingers and in the weight-bearing joints of the knees, hips and spine.

Juvenile rheumatoid arthritis (JRA) can cause severe crippling in children, retard their growth, cause serious emotional and social problems, and, in severe cases, can lead to serious kidney disease, blindness, or death. An estimated 250,000 children under 18 years of age are afflicted with arthritis. It is now clear that JRA is only one of several forms of arthritis in children and adolescents.

Diffuse connective tissue diseases, although less common than degenerative joint disease or rheumatoid arthritis, can involve not only the joints, but also one or more internal organs such as the kidneys, heart, and lungs, sometimes with fatal results.

Systemic lupus erythematosus (SLE), which primarily strikes women of childbearing age, and progressive systemic sclerosis (scleroderma) are two such serious conditions; their causes are unknown, and no cure is now available.

The cost of arthritis in terms of its emotional and social impact is enormous.

Diagnosis is frequently complicated because symptoms are so wide-ranging. The course of the illness is often erratic and victims are subject to spontaneous flare-ups of pain and swelling. Remissions can also occur spontaneously, providing temporary relief for weeks, months or even years.

Arthritis can strike any age group, although the chances increase dramatically with age: 41 percent of persons 65 years of age or older, have arthritis. Several forms of arthritis such as rheumatoid arthritis or lupus are more common in women than in men, although in others such as gout and ankylosing spondylitis (inflammation of the spine), the opposite is true.

The economic costs provide another index to the impact of arthritis. Temporary and permanent disability results in lost wages and tax revenues, and other costs include drug therapy, homemaker services, hospitalization, rehabilitation, unemployment compensation, and research expenditures. A 1975 estimate by the Arthritis Foundation set the cumulative price tag for that year at over $13 billion.

The cause or causes of most types of arthritis are as yet unknown. By the same token, in most types there is no cure.

Methods of treatment such as drugs, physical therapy and surgery have greatly improved the outlook for management of arthritis in recent years. Research efforts of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) have focused on finding the causes of arthritis, improving drug therapy and developing new effective surgical techniques that alleviate arthritic symptoms and improve function.

National Institute of Arthritis, Metabolism, and Digestive Diseases

The elusive nature of the causes of arthritis and most related rheumatic diseases calls for a continuing emphasis on gaining fundamental knowledge through basic laboratory research. An intensive effort is underway by NIAMDD to increase understanding of the nature of arthritis, through research conducted at major universities and medical schools throughout the country, and at the Clinical Center of the National Institutes of Health, Bethesda, Maryland.

The research program supported by NIAMDD continues to focus on expanding

the general understanding of how connective tissue diseases and associated musculoskeletal disorders develop. Basic investigations involve immunology (including autoimmunity and disturbances of immune systems both hormonal and cellular in origin); purine metabolism (relevant to understanding gout); skeletal muscle structure and function; the structure, function, production, biochemistry and physiology of collagen, elastin, and other proteins of connective tissue; and of the constituents of the "ground substance" such as mucopolysaccharides and mucoproteins. Almost two-thirds of the research expenditures of NIAMDD in arthritis are devoted to these fundamental investigations.

Research projects are also in progress to study the specific types of collagen in osteoarthritic cartilage, the effect of motion on the cartilage of the joints, enzyme processes in arthritis, and the mechanics of normal, arthritic, and prosthetic joints.

Multipurpose Arthritis Centers

A central feature of the National Arthritis Act of 1974, and the Arthritis Plan is the concept of supporting Multipurpose Arthritis Centers, located in geographically dispersed areas throughout the U.S.

The purpose of the centers is to demonstrate and promote the application of available knowledge for the treatment of arthritis patients, and to serve as major resources for generating new knowledge and disseminating information on the causes and control of arthritis and related musculoskeletal diseases.

In order to do this, the centers program is organized to provide for activities in three areas: professional and patient education, research, and community demonstration programs.

NIAMDD translated the centers concept into a reality with the initial establishment of 15 Multipurpose Arthritis Centers in 1977. Located in Alabama, Arizona, California, Indiana, Louisiana, Maryland, Massachusetts, Michigan, Missouri, New Hampshire, South Carolina, and Texas, the centers were dispersed throughout the country, as mandated by the National Arthritis Act and the Arthritis Plan. Fiscal Year 1977 funding totaled $2.5 million with an average funding level of $160,000 per center grant.

In 1978, NIAMDD expanded its program to include 9 new centers, while continuing funding support for the original 15 centers. The institutions receiving these new grant awards are: the University of Connecticut School of Medicine, Farmington, Conn.; the Hospital for Special Surgery, New York, N.Y.; State University of New York, Brooklyn, N.Y.; the Medical College of Wisconsin, Milwaukee, Wis.; the University of Missouri School of Medicine, Columbia, Mo.; Vanderbilt University School of Medicine, Nashville, Tenn.; the University of Hawaii John A. Burns School of Medicine, Honolulu, Hawaii; Case Western Reserve University Medical School, Cleveland, Ohio; and the University of Cincinatti Medical College, Cincinatti, Ohio.

A more detailed description of the Multipurpose Arthritis Centers program of NIAMDD is found in the annual centers report.

RESEARCH ADVANCES

Rheumatoid Arthritis

As estimated by the Arthritis Foundation, 6.5 million Americans have rheumatoid arthritis (RA), a chronic inflammatory disease of both the small and large joints of the body. It can also be a systemic disease affecting other organs such as the blood vessels, lungs, heart, or nerves, and its cause is unknown.

The course of the disease may be erratic, characterized by periods of remission and periods when the symptoms flare-up, but overall, rheumatoid arthritis tends to be cumulative, chronic, and is often progressive.

Evidence is accumulating to show that immunologic events play an important role in initiating and maintaining inflammation of the joint tissues. Initially, through a process yet incompletely understood, antibodies are produced by the body against specific tissue components of joints. This is followed by an interaction of the tissue components, acting as antigens, and these abnormal antibodies, leading to the formation of immune complexes.

As the complement system is activated by these complexes, leukocytes are attracted to and then phagocytize (consume) the immune complexes. With this process of phagocytosis, lysozomal enzymes, capable of destroying proteins, are released. It is believed at present that these enzymes destroy articular cartilage.

Now it has been shown that some immune mechanisms in rheumatoid arthritis may be, at least in part, under genetic control. A certain histocompatibility antigen, DW4, has been found in 48 percent of patients with rheumatoid arthritis, as compared to 8 percent in the general population. This antigen is located on that part of the chromosome that is concerned with the regulation of cell-mediated immunity. Newer studies by NIAMDD grantees at Rockefeller University in New York have investigated two interrelated genetic marker systems, B

cell (Ia) alloantigens and the HLA D system, both measures of the major histocompatibility complex.

This study also showed that patients with rheumatoid arthritis have frequencies of these two major histocompatibility complex determinants that are much higher than in normal persons. These determinants are also distinct from those found in systemic lupus erythematosus (SLE). In that disease, the Rockefeller research team found that roughly 70 percent of patients with SLE have increased frequencies of different B cell alloantigens called Ia2 and Ia3. The ability to identify patients predisposed to RA might result in earlier and better treatment and could be important to researchers trying to learn what factors trigger the disease.

Certain of a new group of hormones, prostaglandins, have been shown to be mediators of inflammation in rheumatoid arthritis and to cause bone resorption. The local accumulation of prostaglandin of the E series has been confirmed by studies using indirect immunofluorescence techniques. NIAMDD support has helped to show that prostaglandin is probably being made in rheumatoid synovial lining cells as well as being present in interstitial inflammatory cells. The possibility is carefully being considered that elevations in prostaglandin levels within rheumatoid synovia may represent a paradoxical reaction within the rheumatoid tissue which itself subverts an effective inflammatory response. It is of current interest that many drugs clinically useful for the treatment of rheumatoid arthritis have shown potent anti-prostaglandin activity. If drug-depressed prostaglandin synthesis can bring about the restoration of a balanced and effective immune response, then an explanation will be at hand for the ability of certain drugs to lessen rheumatoid activity.

Massachusetts General's Dr. Henry Mankin is investigating the significance of prostaglandins as potential agents to alter articular cartilage metabolism. The inhibition of the synthesis of certain prostaglandins by nonsteroidal anti-inflammatory agents has implicated prostaglandins in the pathogenesis of inflammatory disease states. Clinical observations have established the anti-inflammatory effects of aspirin and indomethacin in the therapy of rheumatoid arthritis. Recently, Dr. Mankin and his colleagues have discovered that (1) prostaglandins derived from rheumatoid synovium inhibit the metabolism of articular cartilage; and (2) temperature modulates prostaglandin synthesis in cartilage cells in joints.

Treatment in the early stages of RA is designed to relieve pain, to control inflammation, and to prevent deformity. Many cases can be controlled satisfactorily on a program of rest, physical therapy, and salicylate drugs such as aspirin; and do not progress to significant joint destruction or interference with the normal routine of the patient's life. However, many people are not as fortunate, and some cases require treatment with other drugs such as gold compounds or corticosteroids.

The experimental drug D-penicillamine (a chelating agent -- no relation to penicillin) has been reported to be at least as effective as gold compounds in treating rheumatoid arthritis that is sustained, progressive, and unresponsive to salicylates and other anti-inflammatory agents. NIAMDD grantee Dr. Israeli Jaffe of the New York Medical College, New York City, has studied D-penicillamine for a number of years and points out the drug's serious side effects, such as leukopenia and thrombocytopenia (reduction in numbers of white blood cells and platelets, respectively), proteinuria, skin rash, fever, oral ulcers, nausea, alteration of taste perception, and mammary gigantism.

NIAMDD continues to sponsor clinical trials of D-penicillamine in an attempt to interrupt or modify the destructive rheumatic process, and is conducting a major cooperative study with the U.S.S.R. Clinical trials involving large numbers of patients in New York and in Moscow are now underway, using doses lower than those used in earlier trials.

NIAMDD is also sponsoring clinical trials with D-penicillamine through the clinics participating in the Systematic Cooperative Studies Program, coordinated through a contract with the center for Cooperative Studies of Rheumatic Diseases at the University of Utah. NIAMDD grantees from the University of California, San Diego, headed by Dr. Wayne Akeson, are studying the biochemical, bioengineering, and morphologic aspects of the mechanisms of joint contracture. Their data suggest that D-penicillamine is an effective agent in the prevention of severe contracture formation by inhibiting collagen cross-linking reactions. Studies are now in progress to determine whether D-penicillamine can reverse established contracture.

Systemic Lupus Erythematosus

An estimated 50,000 new cases of systemic lupus erythematosus (SLE) are diagnosed each year, indicating that the disease is far more common than it was formerly thought to be. Fortunately, the outlook for this potentially fatal connective tissue disease has improved greatly since 1955, when the survival rate was only 50 percent 4 years after diagnosis. Because of increased awareness of the disease, more sophisticated diagnostic methods, improved drug therapy, and perhaps other factors as yet unidentified, the rate of survival is now over 90 percent 5 years after diagnosis, and over 80 percent 10 years after diagnosis.

SLE is one of the most frequent serious disorders in women of childbearing age, and, in fact, about 90 percent of SLE patients at onset of the disease are adolescent or young women. Recent studies supported by NIAMDD have provided some evidence that estrogens (a class of female sex hormones) may accelerate the development of experimental SLE in certain types of mice. This may help to explain the frequency of the disease in young women. In turn, androgens (male sex hormones) may delay or impede the development of SLE.

Dr. Alphonse T. Masi of the University of Tennessee Center for the Health Sciences, with support from NIAMDD, collaborated with an epidemiologist at DHEW's Center for Disease Control in Atlanta and found mortality from SLE to be four times higher among females than males. Using death certificate data, the researchers found that the death rate rose markedly through the third decade for white females, and it climbed even more steeply for black females in the fifth decade. By contrast, peak elevation of the black male death rate above the white occurred between the ages of 25 and 35. Through the fifth decade, age-specific mortality of the black population remained at least three times higher than that of the white. Following adjustment for the possible influence of overall mortality factors, the female-to-male mortality ratio increased to nearly 10 or higher from the second through fifth decades. These results indicate, therefore, that sex and race are both powerful determinants that interact synergistically to increase risk from SLE in black females of childbearing age.

NIAMDD research investigators Drs. Neil T. Stahl and John L. Decker, NIAMDD Clinical Director, pursued the study of hormonal factors in SLE by assessing the androgenic status of 12 men with SLE. Except for minor abnormalities

explained by treatment or kidney insufficiency, normal hormone levels were found. It did not appear that androgen deficiency was a necessary requirement for the development of SLE in men.

A study that characterized the clinical and humoral immune status of patients with SLE during acute episodes of neuropsychiatric disturbances was carried out by NIAMDD grantee Dr. John B. Winfield, University of Virginia School of Medicine, and his associates Drs. Carol M. Brunner and David Koffler.

The research team found that there was no direct involvement in SLE brain injury by DNA, anti-DNA complexes or lymphocytoxic antibodies. They do suggest an association between a new type of antinuclear antibody (Sm) and central nervous system disease caused by SLE.

Another NIAMDD grantee, Dr. Thomas T. Provost, State University of New York, Buffalo, found that a subset of patients with discoid lupus erythematosus (a relatively benign condition characterized mainly by skin lesions) also had antibodies directed against cytoplasmic antigens and were potentially at risk for the development of the systemic disease.

NIAMDD research investigators at the NIH Clinical Center continue to study the genetic factors in SLE in the effort to identify immune genetic markers associated with SLE. They have found that selective B lymphocyte alloantigens, which are controlled by genes in the major histocompatibility complex, are present in increased frequency in SLE.

Initial research reports in the 1970's indicated that the immunosuppressive agents, azathioprine and cyclophosphamide, would be effective in treating lupus nephritis. However, the results of more than 10 controlled clinical trials since that time have shown that these agents have serious, toxic side effects such as hair loss, bloody cystitis, infections, bone marrow suppression, injury to gonads, and possible malignancy. NIAMDD scientists at the NIH Clinical Center are studying various dosage schedules in the administration of these drugs in order to minimize their side effects while maintaining their effectiveness.

They also have given further study to certain side effects of three of the new nonsteroidal anti-inflammatory drugs -- ibuprofen, naproxen, and fenoprofen. The data obtained confirmed that certain nonsteroidal anti-inflammatory drugs can depress renal function and decrease urinary excretion of prostaglandin

E-like compounds. Careful assessment should be made of renal function in patients receiving drugs which inhibit prostaglandin synthesis.

NIH research scientists and grantees at medical centers throughout the country are continuing their investigations into the immunologic abnormalities in SLE, genetic factors that regulate these immunologic responses, and the development of new approaches to therapy.

Osteoarthritis

More precisely called degenerative joint disease, osteoarthritis is by far the most common form of arthritis, claiming 16 million victims in the U.S. It is characterized by cartilage degeneration and bony overgrowth in joints, with less of the inflammatory response typical of other forms of arthritis.

Encouraging progress is being made through the increased information that has been developed in joint biomechanics, the ultrastructure and chemical composition of cartilage, and experimental models of osteoarthritis in animals.

Refined biochemical techniques, that accommodate minute tissue samples and the ability to correlate tissue changes biochemically with biomaterial qualities, have provided new possibilities for productive studies in this disease. A number of influences, both chemical and physical, that relate to normal and pathologic metabolism of cartilage can be defined. However, the precise and definite role that these influences play in cartilage metabolism and in the development of degenerative joint disease is still undetermined.

Studies using animals with partial meniscectomy (an animal model for osteoarthritis in which the cartilage covering the two opposing bone ends in a joint has been partially removed) and other models that simulate the human disease model have proven helpful in further understanding the components of the osteoarthritis process and in evaluating therapeutic agents.

Two biochemical defects have been identified as bases for the observed aggregation defects of joint cartilage proteoglycans in osteoarthritis. In some cases, there appears to be an abnormality in tissue hyaluronic acid and the proteoglycans are unable to interact normally with high molecular weight hyaluronic acid. In other cases, the aggregation defect appears to reside in the proteoglycans

themselves that are unable to interact with hyaluronic acid in vitro. Separate studies have shown that the breakdown of proteoglycan complexes and collagen fibers in human articular cartilage may be attributed, at least in part, to proteolytic enzymes present in the matrix and presumably derived from chondrocytes (cartilage-producing cells). Collagen is digested by a specific enzyme -- collagenase -- and the proteoglycans may be digested by cathepsin D. It does not appear that cathepsin D can act outside the liposomal system or beyond the cell surface because of its low optimum pH. Evidence has been presented for the presence of a group of metalloproteases of low molecular weight that diffuse through the matrix and digest proteoglycans at neutral pH. The active material from human cartilage has been purified and is activated by cobalt, zinc, and iron.

Dr. Henry Mankin and his associates at Harvard University, working with NIAMDD support, have reported studies in which the enzyme collagenase and an inhibitor of collagenase were found in osteoarthritic cartilage. The findings suggest that degradation of the osteoarthritic surface to the base bone occurs with end-stage osteoarthritis as a result of locally synthesized collagenase. This and other work of these investigators in studying the histology and chemical response of cartilage is serving to help understand the pathogenesis of degenerative joint disease.

A quantitative method for measuring proteoglycan release was devised using bovine nasal cartilage discs and synovial (joint lining) explants in an organ cocultivation system by a grantee, Dr. C. B. Sledge, from the Robert B. Brigham Hospital in Boston. Synovia from human rheumatoid or rabbit antigen-induced arthritis significantly stimulated the release of proteoglycans. These experiments demonstrate that significant degradation of cartilage is induced immediately after the addition of inflamed synovium, and any lag in the response may be due to products that do not readily form ionic complexes.

Psoriatic Arthritis

Psoriatic arthritis resembles rheumatoid arthritis but it has been shown to have the clinical, radiographic and serological features to consider it an independent clinical entity. Psoriasis is not uncommon, and the simultaneous occurrence of psoriasis and arthritis has produced reports of arthritis in 1 to

32 percent of psoriatic individuals.

Psoriatic arthritis is characterized by terminal and proximal interphalangeal joint involvement (as opposed to proximal involvement in rheumatoid arthritis), psoriatic nail changes (pitting, scaling under nails), bone destruction in involved joints in severe cases, sacroiliac involvement, negative tests for rheumatoid factor and absence of rheumatoid nodules (usually found in the skin and subcutaneous tissues of patients with rheumatoid arthritis).

In a study of 100 cases of psoriatic arthritis, the median age of onset was 38 years and the sex ratio was 2:1 (69 percent men and 31 percent women). In 97 percent of the cases, the psoriatic arthritis followed the cutaneous lesions while in the remaining 3 percent of cases the joint lesions preceded or were synchronous with cutaneous lesions.

Psoriatic arthritis appears to be more asymmetrical than rheumatoid arthritis with the onset often affecting single rather than multiple joints.

Lyme Arthritis

A research team at Yale University, headed by NIAMDD grantee and former intramural NIAMDD scientist Dr. Stephen E. Malawista, has found additional information to indicate the source of the mysterious Lyme arthritis. First recognized in 1975 in patients living in three adjacent townships in Connecticut -- Lyme, Old Lyme, and East Haddam -- the disease is characterized by a skin lesion (erythema chronicum migrans) and frequently by inflammatory arthritis in the knee or shoulder. It has now been traced to the bite of the tick, Ixodes scapularis, which transmits the Lyme arthritis agent, presumably a virus.

During the past 3 years, the Yale team has seen over 200 patients in southeast Connecticut, western Rhode Island, Cape Cod, Massachusetts, and Long Island, New York. The disease appears to occur mostly in young people between the ages of 5 and 15 years.

The relevance of Lyme arthritis to an understanding of rheumatoid arthritis has been manifested by the presence of circulating immune complexes in most patients exhibiting the skin lesion.

The treatment for Lyme arthritis has been aspirin during symptomatic

periods, coupled with intra-articular injections of steroids in the most severe cases. However, on the basis of current data, the disease appears to be self-limiting and it is expected that the symptoms will taper off over time, with or without treatment.

Orthopedic Research and Bone Diseases

Basic and clinical studies of the skeleton under normal and disease conditions are the focus of NIAMDD's Bone Diseases program. Projects on calcium metabolism and bone formation, fracture healing and fixation, transplantation and preservation of skeletal tissue, prostheses and related work in biomaterials, biomechanics, and bioelectricity, musculoskeletal dynamics and the physiology of normal and abnormal gait are included in this program.

In addition to an extensive extramural grants program, NIAMDD established an Orthopedics Research Unit at the Johns Hopkins School of Medicine, Baltimore, Maryland, during 1978. This unit is carrying out basic research on bone and connective tissue under a contract from NIAMDD. It is anticipated that the unit will be relocated to the Institute's intramural program in Bethesda, Maryland, when new laboratory and clinical facilities become available at the National Institutes of Health campus.

Through NIAMDD's extramural grants program for bone research, Dr. Carl Brighton and colleagues at the University of Pennsylvania have been studying electrically induced osteogenesis (bone formation) both in animals and in patients with fractures resistant to healing. They have found that precise amounts of electrical current (5-20 microamperes) must be applied to the bone to be effective. Too low a dose induces no bone formation and too large a dose causes local tissue death. Using the principle that the active part of the cathode is limited to the insulation-bare wire junction, a cathode was designed which contained eight such active sites. This device significantly increases the amount of new bone formed and stimulates bone union at fracture sites which were previously resistant to spontaneous bone healing.

Dr. Melvin Glimcher and his colleagues at Children's Hospital in Boston have shown that phosphoproteins of human, bovine, chicken and rabbit bone contain significant amounts of o-phosphothreonine in addition to o-phosphoserine.

This represents the first instance in which o-phosphothreonine has been identified in the structural proteins of mineralized tissues and adds another factor which distinguishes the phosphoproteins of bone from those of dentine and enamel.

NIAMDD grantees at the Mayo Clinic, headed by Dr. Patrick Kelly, have devised an experimental technique to measure small concentrations of radioactively tagged penicillin and gentamicin in canine cortical bone and in the serum of the general circulation after implantation with Palacos R bone cement. These studies show that this cement allows sufficient antibiotic penetration of bone to produce effective levels without toxicity and thus demonstrates the effectiveness of antibiotics incorporated into bone cement. The technique requires a much smaller sample size for experimental determinations, and incorporating antibiotics into bone cement used for restorative procedures may also be useful in controlling bone infections which frequently complicate such repairs.

Dr. David Cohn at the University of Kansas School of Medicine, is studying the actions of 1,25-dihydroxy calciferol ($1,25(OH)_2D_3$) and parathormone, both effective bone-resorptive agents in vivo and in vitro, on osteoclast-like and osteoblast-like bone cells. Data suggest that $1,25(OH)_2D_3$ and parathormone induce bone resorption by affecting the same cells (osteoblasts and osteoclasts), although at different cell sites on the cell surface.

Dr. Leonard Deftos at the University of California, San Diego, has devised a multiple assay system for the hormone calcitonin. He has discovered, with this assay, that (1) low concentrations of calcitonin are secreted in normal adults and (2) in several disease states, abnormal secretion or metabolism of the hormone occurs. These disease states include malignancies, renal diseases, metabolic bone diseases, such as Paget's disease and osteitis fibrosa cystica, and hypercalcemia due to other causes.

Utilizing the hypothesis that osteoporosis, a major health problem for older Americans, is caused by an increased long-term depletion of calcium from bone, a team of investigators headed by Dr. Robert Heaney at Creighton University, has attempted to reverse this loss by improving calcium absorption through increased calcium intake, and found that calcium balance is improved as calcium intake increases. Two commonly used forms of treatment, estrogen/androgen therapy (supplying tissue building sex hormones) and calcium supplementation,

have both shown a decrease in age-related bone loss in patients suffering from osteoporosis.

Research conducted by NIAMDD grantee Dr. Edith M. Carlisle, UCLA School of Public Health, also has implications for the future treatment of osteoporosis. This research demonstrated in organ culture that bone growth is dependent upon the presence of silicon and that silicon is required for formation of the two major bone matrix components, collagen and polysaccharides.

In a study conducted at Children's Hospital, Boston, by Dr. Melvin Glimcher, chemical changes were detected in cartilage after meniscectomy (a surgical procedure which induces secondary osteoarthrosis). These biochemical changes were uniformly distributed throughout the articular cartilage of the knee at 8 weeks, though a focal trend was developing by 12 weeks. This suggested that both altered mechanical stress and biochemical factors are important in initiating the early stages of development of osteoarthritic lesions.

Research into the long-term effects of sodium etidronate (EHDP) in the treatment of Paget's disease of the bone (osteitis deformans) has given preliminary information to indicate that 5 mg of EHDP/kg body weight per day for 6 months appears to be the dose with the lowest risk-benefit ratio. A research team, headed by Dr. M. R. A. Khairi at the Indiana University School of Medicine, Indianapolis, treated 116 patients with diagnosed Paget's disease for from 1 to 46 years. The patients ranged in age from 38 to 82 years.

Artificial Joints

Perhaps the most exciting development in orthopedic research in the past two decades has been the evolution of the artificial hip joint. Hip joint replacement today is one of the most successful orthopedic procedures for restoring mobility to patients, even in cases where previous reconstructive surgery has failed. An estimated 80,000 total hip replacements were performed in the U.S. from May 1977 to May 1978. The artificial knee, the second most frequently replaced joint, is not yet as successful as total hip replacement. NIAMDD is currently increasing its support of investigations into the kinetics, biomechanics, and design and materials for various prostheses for knee and certain other joints.

With an increasing number of replacements being made, especially in younger individuals, the number of failures is increasing. The longer a hip protheses is in use, the more likely it is to wear out at the friction points ("material fatigue"); also, the likelihood increases of a loosening of the prothesis at the points where it is attached with bone cement to the natural bone structures adjacent to the joint. NIAMDD grantee Dr. F. W. Cooke, Clemson University, South Carolina, has conducted research to determine the quantitative influence of variations in surgical techniques on the strength of attachment of the metal femoral head of the prosthetic hip replacement. It is still uncertain whether or not improvements in fixation can reduce fatigue fracture but attempts to improve attachment by cleaning the medullary cavity have been recommended. Greater improvement was obtained by thorough drying of the cavity than by either cleaning alone or the use of thin cement.

NIAMDD grantee Dr. Jonathan Cohen and his associates at Tufts University, Massachusetts, have evaluated failures of orthopedic implants. They have shown that thin rods and plates of vitallium-type cast alloys have superior physical properties to stainless steel, while tensile yield strengths in this alloy excel the levels in all other current types of implants.

When moving parts come into contact, wear occurs. An NIAMDD grantee at the University of Pittsburgh, Dr. Dana Mears, has devised a technique for analysis of wear particles in synovial fluid aspirates of normal and osteoarthritic joints. Wear particles within the synovial fluid specimen often correlate with the rate and mechanism of wear, as confirmed by examination of the joint implant or articular surfaces. This is a useful method of studying both wear rate and the biological response to wear in both arthroplastic and degenerative joints. It holds promise not only as a test for wear and toxicity, but also as a means to assist in the selection of materials and designs for improved articular implants.

OUTLOOK

These examples of research in arthritis, rheumatic diseases, and related disorders of connective tissue and bone are just a few of more than 150 ongoing NIAMDD studies in these fields.

The primary strategy of NIAMDD in its long-range efforts to combat disease, particularly when the cause is unknown, is to support systematic advances of fundamental knowledge in biomedicine. Once the etiology is understood, there is a better chance for more successful clinical management of the disease, and, ultimately, a basis for preventive intervention. The overall goal of NIAMDD continues to be maintenance of a balanced program of basic and clinical research, with special priority emphasis directed toward areas where research progress warrants it.

Recent legislation has put special emphasis on the arthritis program of NIAMDD, requiring expansion and organizational change to meet the challenge of new program responsibilities. The recommendations of the National Commission on Arthritis and Related Musculoskeletal Diseases are vital elements in NIAMDD's strategy to advance fundamental knowledge in arthritis. The Commission summarized what was known about these diseases, and identified knowledge gaps and what was needed to close those gaps, thus providing sound program guidance.

Consequently, highest priorities are being given to research grants in the fields of rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, arthritis in children, and to the study of infectious agents, immunology, infiammation and genetics as they relate to arthritic diseases.

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